CHAPTER 25

Protective role of natural products and bioactive compounds in multiple sclerosis

Gurjit Kaur Bhatti[a], Harsh Vikram Singh[b], Eva Sharma[b], Abhishek Sehrawat[b], Jayapriya Mishra[b], Umashanker Navik[c], P. Hemachandra Reddy[d,e,f,g,h], and Jasvinder Singh Bhatti[b]

[a]Department of Medical Lab Technology, University Institute of Applied Health Sciences, Chandigarh University, Mohali, Punjab, India
[b]Department of Human Genetics and Molecular Medicine, School of Health Sciences, Central University of Punjab, Bathinda, Punjab, India
[c]Department of Pharmacology, Central University of Punjab, School of Health Sciences, Central University of Punjab, Bathinda, Punjab, India
[d]Department of Internal Medicine, Texas Tech University Health Sciences Center, Lubbock, TX, United States
[e]Department of Pharmacology and Neuroscience, Texas Tech University Health Sciences Center, Lubbock, TX, United States
[f]Department of Public Health, Graduate School of Biomedical Sciences, Texas Tech University Health Sciences Center, Lubbock, TX, United States
[g]Department of Neurology, Texas Tech University Health Sciences Center, Lubbock, TX, United States
[h]Department of Speech, Language, and Hearing Sciences, Texas Tech University Health Sciences Center, Lubbock, TX, United States

List of abbreviations

25OHD	25-hydroxyvitamin D
AD	Alzheimer's disease
APP	amyloid precursor protein
BA	butyric acid
BBB	blood brain barrier
CA	caproic acid
CNS	central nervous system
EAE	encephalomyelitis
EBNA	EBV nuclear antigen
EBV	Epstein-Barr virus
EGCG	epigallocatechin gallate
HD	Huntington's disease
HLA	human leukocyte antigen
IFN-β	interferon-beta
IL	interleukin
MCFA	medium-chain fatty acids
MRI	magnetic resonance imaging
MS	multiple sclerosis
PBMC	peripheral blood mononuclear cells
PBMCs	peripheral blood mononuclear cells
PD	Parkinson's disease
PPMS	primary progressive multiple sclerosis

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PRMS progressive-relapsing multiple sclerosis
PUFA polyunsaturated fatty acids
QRC quercetin
ROS reactive oxygen species
RRMS relapsing-remitting multiple sclerosis
SCFA small-chain fatty acids
SNP single nucleotide polymorphism
SOD superoxide dismutase
SPMS secondary progressive multiple sclerosis
TLRs toll-like receptors
TNF tumor necrosis factor
Treg T regulatory cells
WS *Withania somnifera*

Introduction

Multiple sclerosis (MS) is the most commonly occurring disabling neurodegenerative disorder, especially in young adults (Dobson & Giovannoni, 2019). It is also known as disseminated sclerosis or encephalomyelitis disseminate (Koriem, 2016). The central nervous system is affected by this autoimmune, long-term disorder. The name multiple sclerosis means many injuries that occur in the brain including both white and gray matter (McDonald et al., 2001). This disease involves the demyelination of neurons, that is, it attacks myelin which is an insulating sheath present on the neurons. This is due to the death of oligodendrocytes and the infiltration of macrophages and T-lymphocytes (Loma & Heyman, 2011). Consequently, the demyelinated axons, inflammatory cells, and the astrogliosis form the central nervous system (CNS) plaques which interfere with the nerve impulses and lead to decline in the normal neurological functioning (Compston, Winedl, & Kieseier, 2008).

Multiple factors are responsible for causing the disease and include both the genetics and various environment-related factors that play the trigger (Ghasemi, Razavi, & Nikzad, 2017). In the immune system, these factors initiate certain successive events that result in the loss of neurons, gliosis, inflammations, etc., which are other characteristic attributes of multiple sclerosis. In this disease, the central nervous system is exposed to recurrent attacks (Goldenberg, 2012). The symptoms might occur and then completely disappear with the advancement of the disease (Lublin & Reingold, 1996). Other common symptoms include weakness, sensory loss, mood swings, cognitive decline, disturbed bowel functions, loss in vision, etc. (Loma & Heyman, 2011).

Multiple sclerosis has four major forms depending on its occurrence in an isolated neurons, which is the relapsing type or in a cluster of neurons known as the progressive type (Lublin & Reingold, 1996). First is the relapsing-remitting multiple sclerosis or the RRMS. In this, a relapse, which is an acute attack, of symptoms is observed. It is then followed by disappearance of the symptoms. It is the most common type (Weiner, 2008).

Second clinical form is the secondary progressive multiple sclerosis or the SPMS. It is considered a second phase and usually happens to patients who already had a relapsing-remitting course. There is a gradual worsening of the symptoms, and no more relapse is seen. The third type is the primary progressive multiple sclerosis or the PPMS in which there is no relapse or remission and the symptoms continue to worsen from the very beginning. The fourth clinical type is the progressive-relapsing multiple sclerosis or the PRMS. It is relatively rare form and involves a steady decline in neurological functions. Relapses occur, but a gradual increase in symptoms is observed (Goldenberg, 2012; Loma & Heyman, 2011).

There are several biomarkers for MS like IL-6, osteopontin, fetuin-A, nitric oxide, and tetraspanin-32 (Apostolopoulos & Matsoukas, 2020; Koriem, 2016). Downregulation of the tetraspanin-32, which is involved in the immune responses, was observed in T memory cells, encephalitogenic T cells, myelin-specific T memory cells, and the PBMC or the peripheral blood mononuclear cells (Basile et al., 2020). Most of the treatments for MS focus on improving the neurological functioning as well as stopping the progression of the disease (McDonald et al., 2001). Accepted treatments for MS include mitoxantrone, alemtuzumab, natalizumab, INFβ-1a, INFβ-1b, glatiramer acetate, etc., along with complementary therapies like acupuncture, vitamin D treatment, antioxidant compounds, oxygen therapy, yoga, and reflexology. Multidrug therapies are thought to be effective and can further provide novel sources of treating the disease (Koriem, 2016). The diagnosis of MS is done on the basis of the signs and symptoms the patient is showing. There are several criteria that are based on the demonstration of the lesions, and they help distinguish MS from other similar diseases (Poser et al., 1983). The dissemination of the lesions is studied via lab imaging and MRI. MRI helps to detect the plaques in the brain (Huang, Chen, & Zhang, 2017).

Epidemiology of MS

As of the year 2020, over 2.8 million people in the world are affected by MS, and with rising global population, these numbers are expected to surge even more (Walton et al., 2020). The penetrance of this disease in women who are susceptible has been found to be greater than it is in men (Goodin, Khankhanian, Gourraud, & Vince, 2021). In some of the countries, this ratio of affected women to men is 4:1 (Walton et al., 2020). Although, in patients who are above 50 years of age, MS is observed equally in males and in females (Miller & Leary, 2007). The prevalence of this disease is about 120 per 100,000 individuals although it varies with different geographical regions (Holloman, Ho, Hukki, Huntley, & Gallicano, 2013). MS is especially widespread in the northern part of Europe, and the rate is about 200 per every 100,00 individuals (Milo & Kahana, 2010), the reason being vitamin D deficit due to lesser exposure to sunlight (Koriem, 2016) as vitamin D levels are related to the genes associated with MS (Pakpoor & Ramagopalan, 2014). The prevalence in Africa is 0.5 per 100,000 individuals, in the United States of

America it is 8.3 per 100,000 individuals, and in South-East Asia the rate is approximately 2.8 per 100,000 persons (Marrie, 2004; Milo & Kahana, 2010). The RRMS is most prevalent type of MS and is found in about 87% of the total cases of the disease (Weiner, 2008). About 10%–15% of the patients have PPMS type of MS. Approximately 65% of the patients having RRMS also develop SPMS. PRMS is the rarest of all the subtypes and is found in about 5% of the total patients (Ghasemi et al., 2017). Young and adults of middle age are mostly affected by this disabling disease (Ds, 2018). It is majorly diagnosed in the age of 20–40 years. Childhood cases of MS account for about 1% of the cases and about 2%–10% of the diagnosis is found above the age of 50 years (Boiko, Vorobeychik, Paty, Devonshire, & Sadovnick, 2002).

Pathophysiology of MS

MS is an autoimmune disease, and therefore, a number of different pathways associated with the immune system have been explored which play a vital role in this disease (Loma & Heyman, 2011). Fig. 1 shows the pathophysiology of MS. Demyelination by the immune cells and inability of cells to form new myelin sheaths are the two main mechanisms which cause MS (Nakahara, Maeda, Aiso, & Suzuki, 2012). This is followed by formation of lesions in the CNS, and these mechanisms together are responsible for MS (McDonald et al., 2001). With demyelination, inflammation occurs synergistically. The demyelination causes the release of higher levels of antibodies as well as cytokines which damages the blood-brain barrier (BBB) and activates certain destructive proteins. This inflammation is caused by the T cells that enter the brain by disrupting the BBB. These cells, called as the autoreactive lymphocytes, start attacking the myelin sheath of the neurons as they treat it as a foreign entity (McDonald et al., 2001).

Th type1 cells, Th type 17 cells, CD8+ T cells, and the auto-antibody-secreting cells are various inflammatory cells that are involved in this disease (Katsara & Apostolopoulos, 2018). Some pathogen-associated molecules happen to bind to the TLRs or the toll-like receptors on the antigen-presenting cells and secrete cytokines such as IL-12, IL-23, and IL-4, which induce the differentiation of the CD4+ T-cells (Ghasemi et al., 2017). As a response to the specific cytokines, the inflammatory cells get polarized and Th1 release cytokines which are proinflammatory in nature like interferon-gamma. They do this by suppressing the differentiation of the Th2 cells that are responsible for producing anti-inflammatory cytokines such as IL-4 and IL-13 (Zhu & Paul, 2008). Th17, which is a CD4+ T cell, produces IL-17, IL-21, IL-22, and IL-26 (Loma & Heyman, 2011). The receptor for IL-17 has been observed in both acute and chronic MS plaques (Komiyama et al., 2006). The Th1 and the Th17 cells then migrate to the CNS where further demyelination as well as axonal loss is observed (Gandhi, Laroni, & Weiner, 2010).

The Treg or T regulatory cells are another type of cells that are involved in MS (Loma & Heyman, 2011). In normal cells, the function of the T-regulatory cells is to regulate the Th1 and Th17 cells, but in patients suffering from MS, it has been observed that

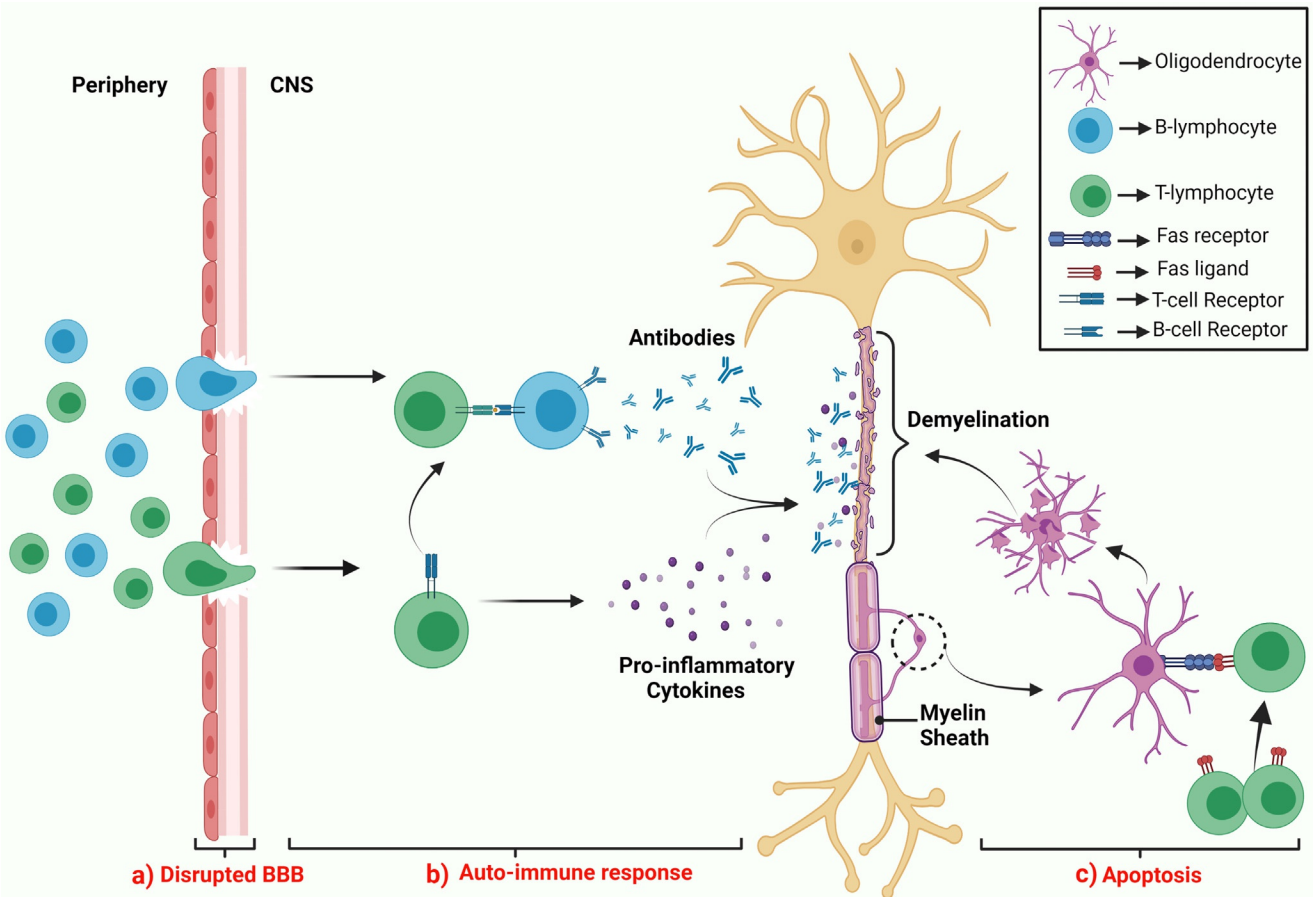

Fig. 1 Pathophysiology of MS. This figure depicts the process of demyelination, a major characteristic of MS (A) represents disruption of BBB as a result of various factors including injury, bacterial or viral infections; and subsequent infiltration of B and T-lymphocytes into the CNS parenchyma; (B) the activation of T-lymphocytes by the APCs thus triggers release of proinflammatory cytokines; and interaction between B-lymphocytes and T-lymphocytes further leads to auto-immune attack; (C) destruction of oligodendrocytes via the Fas-Fas ligand system where T-lymphocytes producing the Fas ligand binds to Fas receptors on oligodendrocytes and mediates their apoptosis. *Figure created in Biorender.com*.

T regulatory cells exhibit a reduced function (Haas et al., 2005). The CD8+ T cells also have a possible role in the progression of MS as they have been found in the MS lesions. The CD8+ cells also expose the axons by killing the surrounding glial cells. They also activate the death of oligodendrocytes (Kasper & Shoemaker, 2010). Not just T cells even B cells are involved in MS. Apart from secreting proinflammatory and anti-inflammatory cytokines (Duddy et al., 2007), the brain of MS patients also showed presence of B cell follicles (Magliozzi et al., 2007). The lymphocytes produce the Fas ligand for the FasL which binds to a cell surface receptor of the TNF receptor superfamily called the Fas receptor which is present on the oligodendrocytes which start the apoptosis of these cells. Consequently, the production of myelin sheath gets impaired due to a reduction in the number of cells which are responsible for synthesizing myelin sheath (Li et al., 2002).

Oligodendrocytes are responsible for the formation of the myelin sheath around the axons of the nerve cells. The myelin sheath is an insulating covering, which helps in passing on the neural signals in the body. These oligodendrocytes get destroyed in MS, and consequently, there is a destruction of myelin around the nerve axons, and this interferes with normal signal transfer among the neurons (McDonald et al., 2001). The cells are unable to form new sheaths, and lesions cover the damaged nerve axons and are accountable for the symptoms that are associated with MS (Chari, 2007). The demyelination is known to follow certain patterns which include hypoxia like injury of the tissue as well as antibody and complement-associated changes. These are initiated by a loss in polarity of the astrocytes and also due to the death of oligodendritic cells (Zindler & Zipp, 2010).

Risk factors associated with MS pathology

The major cause of injury in MS is the inflammation of the CNS which is caused by a number of genetic as well as environmental factors (Fig. 2). Apart from the genetic disposition, there are several other factors including bacterial and viral infections (Savarin, Bergmann, Gaignage, & Stohlman, 2015), smoking, pollution and stress (Ascherio & Munger, 2007) that might be associated with the pathophysiology of the disease.

Genetic factors

The human leukocyte antigen or the HLA, Class II and I alleles are the major susceptibility alleles that can lead to development of MS. The main haplotype contributing to the susceptibility is the haplotype HLA DRB15:01 (Waubant et al., 2019). The gene products that are responsible for presenting antigens to CD4+ T cells are encoded by class II variants, while the ones that present antigens to CD8+ T cells are encoded by the class I variant. Some of other genetic factors include some non-HLA SNPs that happen to modulate the risk of developing MS (Olsson, Barcellos, & Alfredsson, 2017). Genetic variants are also involved by their combined effect with environmental factors. A higher risk of MS is observed when polymorphisms occur near to CYP27B1 gene,

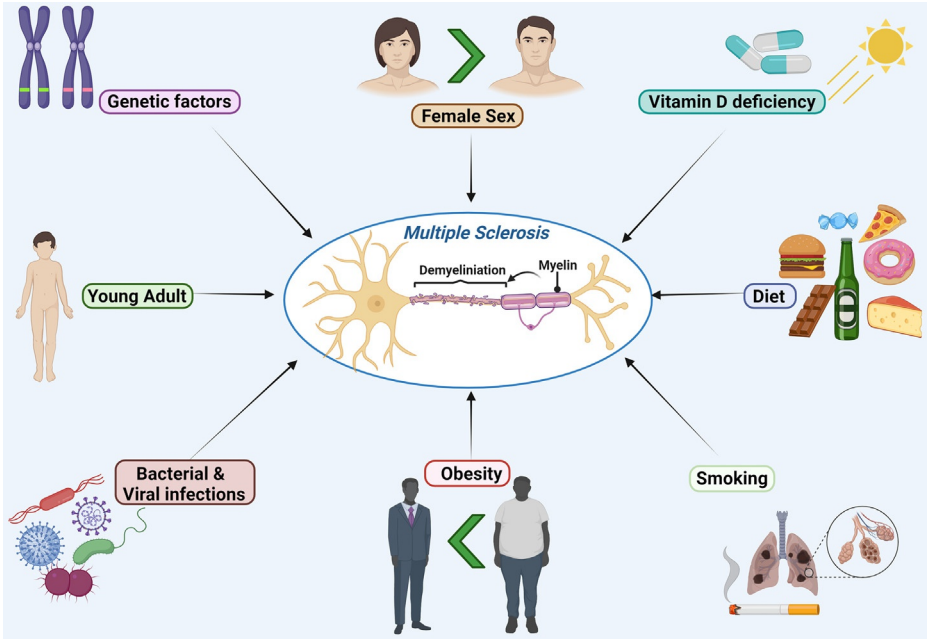

Fig. 2 Risk factors associated with MS. The multifactorial nature of MS as suggested by various epidemiological studies includes genetic as well as other environmental factors. Low vitamin D levels, unhealthy diet, and lifestyle predisposes to MS. *Figure created in Biorender.com.*

which encodes for the main enzyme responsible for the metabolism of Vitamin D (Beecham et al., 2013).

Vitamin D deficiency

Several studies have proved that lower vitamin D, which is the blood concentration of 25-hydroxyvitamin D or the 25OHD, elevates the risk of MS (Ha-Vinh et al., 2016). Lesser exposure to sun in childhood, and even in the later stages, increases the risk of developing MS (Lucas et al., 2011b). Both ultraviolet radiations and vitamin D are known to have protective affects against MS. An increased exposure to ultraviolet radiation significantly decreases the risk of developing MS (Lucas, Byrne, Correale, Ilschner, & Hart, 2015). In individuals with a lower exposure to sunlight, a diet rich in vitamin D provides protection and a lower risk of developing MS (Bäärnhielm, Olsson, & Alfredsson, 2014). High levels of vitamin D content in the body are also related to a decrease in the axonal damage in the patients suffering from MS (Sandberg et al., 2016).

Viral infections

A lot of researches have established the role of viral infections in MS. The main evidences being demyelination of neurons induced by viruses and the oligoclonal bands that are found in the CNS fluid in patients suffering from MS (Gilden, 2005). Epstein-Barr virus

(EBV) infection is associated with an increase in risk of MS (Belbasis, Bellou, Evangelou, Ioannidis, & Tzoulaki, 2015). EBV might be associated with MS through the gene transcription alterations induced by EBNA-2. EBNA (EBV nuclear antigen) is also known to interact with HLA-A02 (Lucas et al., 2011a). The susceptible HLA alleles that are responsible for regulating the T cells adaptive immunity and their interaction with the EBV might be the cause of the common molecular pathways that cause MS (Hedström, Lima Bomfim, Hillert, Olsson, & Alfredsson, 2015). Interaction between DRB1 and EBV status is also known to alter the risk of MS (Xiao et al., 2015). RNA related to EBV has been found in the lymphoid infiltrates of the central nervous system (Serafini et al., 2007).

Smoking

Smoking of cigarettes is major risk factor for the development of MS (Poorolajal, Bahrami, Karami, & Hooshmand, 2017). However, people who quit smoking exhibit a decline in the excess risk of MS (Hedström, Hillert, Olsson, & Alfredsson, 2013). The risk of MS and smoking have a dose-response relationship (Hedström, Bäärnhielm, Olsson, & Alfredsson, 2009). Smoking triggers the inflammation in lungs and is also responsible for promoting pathways that are proinflammatory (Shan et al., 2009). The auto-antigenic cells that are present in the lungs possibly get activated and attack the central nervous system by acquiring a migratory phenotype (Odoardi et al., 2012). Not just active but also passive smoking is known to increase the risk as it causes lung irritation (Abdollahpour et al., 2017). Air pollution is also responsible for neuroinflammation in the CNS and is a risk factor for MS (Heydarpour et al., 2014). Smoking not only elevates the risk of MS onset but it also neutralizes the effect of treatment which uses natalizumab and IFN-β (Hedström et al., 2014).

Obesity

Obesity is known to increase the risk of onset of MS by two folds (Gianfrancesco et al., 2017). This relation is found to be more prominent in females as compared to males (Liu et al., 2016). Adolescence is a very critical period wherein the weight and BMI usually dictate the risk of developing MS in adulthood (Hedström, Olsson, & Alfredsson, 2016). Like other factors, BMI also interacts with the HLA risk alleles. Individuals with a high BMI do not show the presence of the protective HLA-A*02, which increases the risk of MS by about 14 times (Hedström et al., 2014). Obesity is also associated with an increase in the levels of proinflammatory molecules that are produced in the fat tissue and cause inflammation (Lumeng, Bodzin, & Saltiel, 2007). Obesity is also known to be responsible for decreasing the bioavailability of Vitamin D (Matarese, Carrieri, Montella, De Rosa, & La Cava, 2010).

Therapeutic strategies

Several pharmacological drugs, currently undergoing clinical trials, are targeting the molecular mechanisms of MS pathology. However, effective treatment of MS is still not available. Following are the possible therapeutic drugs that are used for the treatment of MS.

Interferons

Interferon-β (IFN-β) is widely used, FDA approved treatment for MS. IFN-β has proved instrumental in decreasing the progression of disability, reducing the relapse rate, and MRI evidence of the activity of the disease (Loma & Heyman, 2011). IFN-β inhibits the activation and proliferation of T cells, reduces the activity of matrix metalloproteinases, and increases the production of anti-inflammatory cytokines and reduces the formation of proinflammatory cytokines (Dhib-Jalbut & Marks, 2010). There are a number of IFN-β products available in the market. IFN-β has a number of side effects that include headache, fatigue, flu, inflammation at the injection site, and even depression (Borden et al., 2007).

Glatiramer acetate

Glatiramer acetate is used for the treatment of RRMS. It shows effects on the MRI clinical assessment and exacerbation rate (Loma & Heyman, 2011). Glatiramer acetate is known to increase the anti-inflammatory action by increasing Foxp3 expression in CD4+ and CD25+ T regulatory cells. Glatiramer acid also increases the levels of regulatory cytokines such as IL-10, IL-4, and TNF-α (Racke, Lovett-Racke, & Karandikar, 2010). It also shows its effect on CD8+ cells and fix their regulatory deficit (Tennakoon et al., 2006). It also prevents the T cells specific to human myelin basic protein from lysing the targets. Side effects include dyspnea, palpitations, and chest tightness (Racke et al., 2010).

Monoclonal antibodies

Natalizumab

This antibody is FDA-approved and is designed especially for the treatment of MS (Loma & Heyman, 2011). It targets the CD49 molecule and prevents the adhesion of immune cell and endothelial cell blocking the leukocyte migration into the CNS. It has positive effects on relapse rate, MRI activity, and progression of disability (Brown, 2009).

Alemtuzumab

This antibody targets CD52, which is found to be expressed in natural killer cells, B cells, T cells, macrophages, etc., and causes their depletion. This stabilizes the blood-brain barrier and decreases the contrast enhancing lesions in MS (Alireza, Alexander, Mohammad

Ali, & Robert, 2010). It has some serious side effects that limit its use and include various antibody-mediated autoimmune diseases (Coles et al., 2008).

Rituximab and Daclizumab

Rituximab targets CD-20, which is found only on B cells, and it shows its action by depleting B cells (Hauser et al., 2008). Daclizumab targets CD25 cells (Liu, Wang, Zhan, & Xia, 2012).

Cytotoxic agents

Cyclophosphamide

It is a synthetic agent that targets CD45+ and CD4+ cells (Vollmer, Stewart, & Baxter, 2010). It gets activated in the liver and forms cross-links with DNA. It is used for the treatment of RRMS and has a number of side effects including carcinomas (La Mantia, Milanese, Mascoli, D'Amico, & Weinstock-Guttman, 2002).

Mitoxantrone

It is another synthetic agent that intercalates with the DNA of the patients. It is responsible for stopping the migration of monocytes and lymphocytes. It also reduces the proinflammatory cytokine release and promotes the apoptosis of the dendritic cells (Vollmer et al., 2010). Cardiovascular risks, nausea, and bone marrow suppression are its side effects (Loma & Heyman, 2011).

Methotrexate

It inhibits the dihydrofolic acid reductase, consequently inhibiting the DNA, RNA, and protein synthesis. It also reduces the inflammation by inhibiting the production of lymphocytes. It is used for the treatment of RMMS (Gray, McDonnell, & Forbes, 2004).

Natural products

In the absence of any effective pharmacological treatment, a greater emphasis has been placed on the implementation of nonpharmacological interventions that may play preventive role against the MS pathology. The pathophysiological complications associated with MS such as hyper-oxidative stress, spiked autoimmune response, and neuroinflammation can be tackled utilizing diet rich in natural products and bioactive compounds such as polyphenols, carotenoids, vitamin D, niacin, and polyunsaturated fatty acids (PUFAs). Fig. 3 shows the use of various plant-derived bioactive compounds as therapeutic strategy in MS.

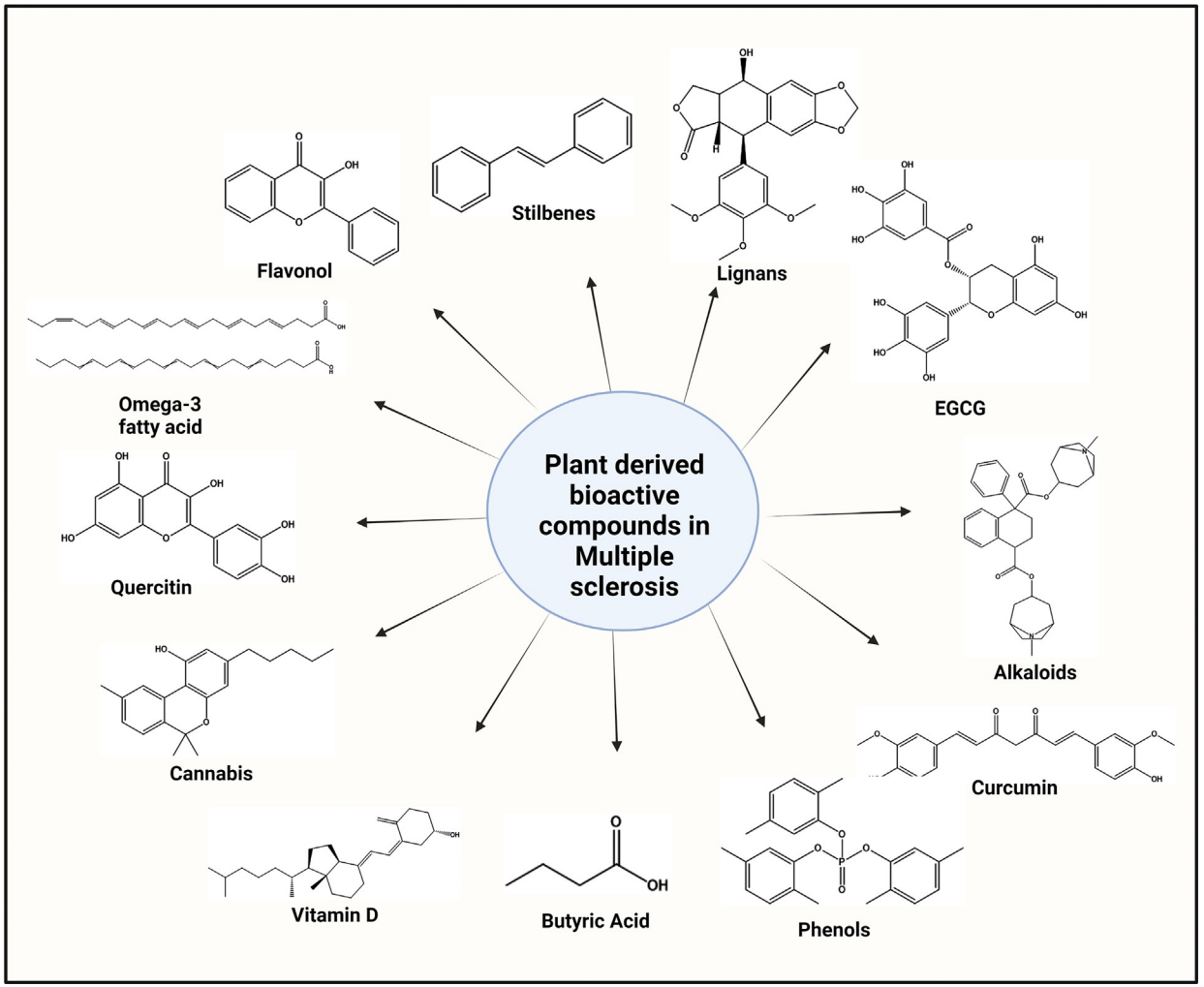

Fig. 3 Bioactive compounds with therapeutic potential in MS. Medicinal plants have proven pharmacological effects against neurological disorders, as evidenced by recent studies. Plant-derived natural products have also shown a positive impact in amelioration or prevention of MS by reducing the demyelination or improving the remyelination of neurons.

Diet

Unhealthy eating is an important risk factor for MS. In 1950, Swank advocates the incidence and severity of MS with the consumption of diet rich in saturated fatty acids, where their digestion and later assimilation produce chylomicron. These chylomicron clumps together to form aggregates, which due to their large size and rigidity, get lodged up in the capillaries causing starvation and multiple scattered lesions in the tissue ahead. They also activate the CD14/TLR4 receptor complex and promote concentration of C reactive protein in blood and upregulate the synthesis of TNFα. These alterations in the physiology of CNS promote the risk of MS. Thus, promoting diet lacking saturated animal fats, containing maximum of 10–15 g of saturated fat can ease the severity of MS and in early ages can even lower the risk to develop MS (Swank, 1950; Swank & Goodwin, 2003).

Omega-3 fatty acids supplementation and fish oil have been shown to improve the quality of life of MS patients These positive effects on inflammatory indicators such as glutathione reductase are credited with these health benefits. They have been demonstrated to lower relapse rates and achieve balanced omega-6/omega-3 ratios (AlAmmar et al., 2021). In a clinical trial, the combined supplementation of vitamin D and omega-3 fatty acids to MS patients was shown to have improvement in concentration of C-reactive protein, total antioxidant capacity of plasma, glutathione level, and concentration of malondialdehyde with improvement in insulin sensitivity and serum HDL-cholesterol concentration (Kouchaki et al., 2018).

Butyric acid (BA) is a short-chain fatty acid, it helps to maintain the integrity of the intestinal membrane credited to its anti-inflammatory. Caproic acid (CA), as well as other medium-chain fatty acids (MCFA) increases TH1 and TH17 differentiation, responsible for neuroinflammation in MS. The level of BA was decreased in MS, whereas the concentration of CA was raised. The microbiota was simultaneously reduced of BA manufacturer microbes and get increased with proinflammatory components which cause mucin- degradation. Decreased serum BA concentrations in MS patients were linked to changes in permeability of barrier, as indicated by increased concentrations plasma consisting of fatty acid-binding protein and lipopolysaccharide in intestine as well as inflammation. CA was shown to be positively linked with T lymphocytes (CD4+/IFN+), while the BA to CA ratio was found to be favorably associated with CD4+/CD25high/Foxp3+ T lymphocytes and negatively associated with T lymphocytes (CD4+/IFN+). The dysbiosis of the gut microbiota observed in MS may be linked to changes in the intestinal barrier and the ratio of SCFA to MCFA, which may explain the persistent inflammation and thus the illness. Quantification of SCFA and MCFA may be a straightforward biomarker for assessing the effectiveness of treatment and rehabilitative methods in MS (Saresella et al., 2020). It was discovered that a higher consumption of PUFA is linked to a reduced risk of MS. Only α-linolenic acid was shown to be

negatively related to MS risk among the different kinds of PUFA. Also the eicosapentaenoic acid and docosahexaenoic acid shown no significant risk toward MS (Bjørnevik, Chitnis, Ascherio, & Munger, 2017).

Polyphenols

The polyphenols credited to their rich antioxidant property and neuroprotective nature can be employed in the diet of MS patients to control the neuroinflammation and neuronal damage due to ROS (Offen, Gilgun-Sherki, & Melamed, 2004). Polyphenols consist of flavonoids and nonflavonoids compounds, where flavonoids include bioactive compounds such as genistein, catechins, and quercetin, and the nonflavonoids consist of curcumin, hydroxytyrosol, and resveratrol (Riccio, 2011). The epigallocatechin gallate (EGCG) is a polyphenolic compound and main catechin found in green tea, reported in several studies for its neuroprotective action, like in a study on Alzheimer's disease, it was shown that treatment with EGCG increases the cell viability, reduces the ROS concentration, and downregulated the Caspase 3 level. It was also reported to activate α7nAChR and its downstream signaling pathway molecule PI3K and Akt, thus downregulating the Bcl-2 in neurons (Zhang et al., 2014).

The ability of EGCG to penetrate the human BBB and protecting cultured neurons via cortical tissue against stress-induced due to ROS leading to apoptosis was shown in a study on optimized human BBB model (Pogačnik et al., 2016). The EGCG also was reported to inhibit Bax3, assisting cytochrome translocation, upregulating LC3-II level, and promoting autophagic pathway, blocking p62 through siRNA ATG5 and exhibiting neuroprotective effect through the assistance of Class III histone deacetylase (Lee et al., 2015). The EGCG is also known for its role in promoting biogenesis of mitochondria, regulating metabolism, cell cycle, and apoptosis via mitochondria (Oliveira, Nabavi, Daglia, Rastrelli, & Nabavi, 2016).

Turmeric contains curcumin, as a main component. Curcumin is renowned for its medicinal properties; few of these properties may be beneficial in the treatment of MS, particularly its anti-inflammatory properties via reduction of proinflammatory cytokine production (Ghanaatian et al., 2019). In a study on astrocytes tissue of rat and serum of MS patients, the flavonoids such as quercetin and catechins and nonflavonoids tyrosol and resveratrol extracted from Green tea, was able to cross the BBB and shown inhibitory effect on the activity of MMP and expression in MS (Liuzzi et al., 2011).

Quercetin is (3,3′4′,5,7-pentahydroxy flavone) belonging to the flavonoid family of polyphenols. It may be found in a variety of fruits, vegetables, and grains; red onions and apple, and wine are two examples of foods high in quercetin. QRC inhibits the production of IL-1, TNF-α, and MMP-9 by peripheral blood mononuclear cells (PBMCs) level thus reduces the MMP-9/TIMP-1 ratio and has anti-inflammatory, immunomodulatory, and antiviral effects (Sternberg et al., 2008). QRC crosses the blood-brain barrier,

suppresses myelin phagocytosis (Hendriks et al., 2003), inhibits the ROS production by astrocytes due to interleukin-1β and from macrophages, controls the production of inflammatory cytokines by inhibiting NF-κB (Min et al., 2007), Flavonoids have neuroprotective properties and protect against IL-1-induced astrocyte-mediated neuronal damage by increasing the ability of activated astrocytes to remove free radicals, lowering the production of proinflammatory cytokines and chemokines, and increasing the ability of activated astrocytes to remove free radicals (Sharma et al., 2007; Youdim, Qaiser, Begley, Rice-Evans, & Abbott, 2004). Following the intake of quercetin, the activity of myeloperoxidase and nitric oxide in the serum, as well as the level of lipid peroxidation in the brain tissues of ameliorating experimental autoimmune encephalomyelitis (EAE) rats, were significantly higher in EAE rats compared to normal control rats, indicating that it could be used to treat MS patients (Mirzazadeh, Khezri, & Abtahi Froushani, 2019).

Cannabis

Several studies have been published on the effectiveness of cannabis in the treatment of MS. Cannabis use may have a variety of benefits, including spasticity alleviation, reduces depression, pain relief, and protection from anxiety. The G-protein-coupled receptor CB1 inhibits adenylate cyclase and controls Ca^{2+} and K^{+} channels. Other routes, such as the inositol phospholipid pathway, may interact with the receptor. CB1 receptors are found mostly in the CNS (especially the cerebellum, hippocampus, and basal ganglia). CB1 receptor activation in the CNS has the overall effect of suppressing neurotransmitter release (Fragoso, Carra, & Macias, 2020). Smoked cannabis was shown to be better than placebo in reducing symptom and discomfort in those with treatment-resistant spasticity in a research (Corey-Bloom et al., 2012). In a cross-sectional research, however, it was shown that inhaling or ingesting street cannabis for an extended period is linked to worse cognitive function in MS patients. Patients' perceived advantages from taking street cannabis, such as pain and spasticity alleviation, should be balanced against the cognitive adverse effects (Honarmand, Tierney, O'Connor, & Feinstein, 2011).

Vitamin D

Vitamin D produced primarily by human skin in response to ultraviolet B exposure; vitamin D insufficiency is linked to a variety of chronic illnesses. Vitamin D insufficiency is thought to be an environmental risk factor in case of MS, and some trials have utilized it as a treatment for the disease. It was shown that a genetically reduced 25-hydroxyvitamin D (25(OH)D) level is linked to an enhanced risk of MS, whereas its supplementation in diet can help to postpone or prevent MS (Mokry et al., 2016). Vitamin D treatment increased serum TGF1beta, IL-10, CD4+ T cells, and decreased the IFN-γ/IL-4 ratio and CD4+ T cells in MS patients. The evidence for vitamin D's immune-modulating

effects is backed up by this anti-inflammatory cytokine profile (Mahon, Gordon, Cruz, Cosman, & Cantorna, 2003; Smolders et al., 2010). The presence of a relationship between high 25(OH)D levels and a lowered risk of MS was seen in the research evaluating the link between 25-hydroxyvitamin D levels and the risk of MS. Decreasing 25(OH)D levels in the community has been found to contribute to the rising MS incidence, which is also confirmed by epidemiologic research (Salzer et al., 2012).

Vitamin B

The brain, neurons, blood cells, and many other areas of the body require vitamin B12 for optimal function and growth. Vitamin B12 is sometimes known as "cobalamins" since it comprises the element cobalt. The metabolically active forms of vitamin B12 are 5-deoxyadenosylcobalamin and methyl-cobalamin Two more forms, hydroxycobalamin and cyanocobalamin, become physiologically active after being converted to methyl-cobalamin or 5-deoxyadenosylcobalamin. Vitamin B12 is required for the correct development, myelination, and function of the CNS, as well as the creation of healthy red blood cells and synthesis of DNA. Vitamin B12 is required as a cofactor for both L-methylmalonyl-CoA mutase and methionine synthase. Methionine synthase converts homocysteine to the important amino acid methionine. *S*-Adenosylmethionine is a ubiquitous methyl donor that may be found in many substrates such as RNA, DNA, proteins, and lipids (Allen, 2012; Institute of Medicine, 1998).

The inflammatory and neurodegenerative pathogenesis of MS and vitamin B12 deficiency are similar. This makes distinguishing between vitamin B12 insufficiency and MS challenging. The connection between blood folate levels, vitamin B12, and homocysteine in individuals with MS was investigated in a meta-analysis research. Patients with MS had higher homocysteine levels but lower B12 levels, which might play a role in MS etiology (Zhu, He, & Liu, 2011). In a research, six patients with chronic progressive MS, who had an extensive demyelination in the central nervous system, were given a large dosage of methyl-cobalamin (60 mg per day for 6 months). Even though the motor disability did not improve clinically, the visual and auditory potential abnormalities improved throughout the therapy. Researchers feel that a high-dose methyl-cobalamin treatment might be useful as an adjuvant to immunosuppressive medicine for persistent progressive MS as a result of these findings (Kira, Tobimatsu, & Goto, 1994).

Biotin, commonly known as vitamin B7, is engaged in a wide range of metabolic activities in both humans and other species, with a focus on fat, carbohydrate, and amino acid metabolism. Several studies have shown that high-dose biotin might be used to treat people with progressing MS. High dosage biotin supplementation to MS patients was shown to be safe and well tolerated in a trial; however, there was no evidence of long-term benefit. More than a third of patients deteriorated while taking biotin, most likely as a result of their illness, while several patients who worsened recovered after

quitting biotin (Birnbaum & Stulc, 2017). Also, in MS patients treated with a high dosage of biotin, thyroid hormone levels were found to be greater in plasma samples, with higher free thyroxine and reduced thyroid-stimulating hormone. As a result, it's possible that high-dose biotin treatment for MS interferes with thyroid assays (Minkovsky et al., 2016).

Honeybee venom

Apitherapy is a field of medicine concerned with the health and therapeutic benefits of honeybee-produced compounds. Bees have long been prized for their therapeutic properties. Bees were believed to have anti-inflammatory properties, aid digestion, and replenish essential humors in the body. The scientific study of bee stings did not commence until the late 1800s. In his medicinal procedures, the father of medicine, Hippocrates, employed crushed bees and bee stings. The current study of apitherapy is believed to have begun in 1888, with Austrian physician Phillip Terc's "Report on a Peculiar Connection between Bee Stings and Rheumatism" (Hauser et al., 2001; Hoyt, 2015).

Bee venom is made up of a variety of ingredients having potential therapeutic properties. It includes 18 active ingredients, the most important of which is mellitin which is around 40%–50% of total, which has anti-viral, anti-bacterial, and anti-inflammatory properties. Apamine enhances cortisol production in the adrenal gland and constitutes 2%–3%. Adolapine (0.5%–1%) is an analgesic and anti-inflammatory, and it inhibits the enzyme cyclooxygenase. Histamine is responsible for the stings' agony and swelling and constitutes 0.5%–2%, 0.2%–1% is Dopamine, 0.5%–1% is serotonin, and 0.5%–1% is norepinephrine, these are all neurotransmitters found in bee venom. The enzymes hyaluronidase constituting 1%–2% and phospholipase A2 constituting 10%–12%, which activate immune cells and generate immunoglobin E, are responsible for the allergic reaction. Mast-cell degranulating proteins soften tissues and allow fluid to flow more freely. Protease inhibitors (0.1%–0.8%) are anti-inflammatory and anti-bleeding medications (Eze, Nwodo, & Ogugua, 2016). According to the findings in a study, therapeutic bee-venom injections on MS patients are effective in reducing dysfunction caused by the disease. Over the course of a 12-month experiment utilizing bee venom, substantial improvements in bowel and bladder control, coordination and body balance, upper and lower limb strength, endurance, tiredness, numbness, and spasticity were seen (Hauser et al., 2001).

In a research to see how honeybee venom affects Lewis rats with Experimental Allergic Encephalomyelitis (EAE), which is a model for MS. The bee venom treatment reduced symptoms such as demyelination of neurons in CNS, infiltration of inflammatory cell in CNS, and decreased the concentration of serum nitrates and TNF-α (Karimi et al., 2012).

In contrast to the previous study, in another randomized, crossover trial with 26 individuals with relapsing progressive MS found the opposite. There was no significant reduction in the cumulative number of new gadolinium-enhancing lesions during bee sting treatment. The relapse rate remained unchanged. Disabilities, tiredness, and quality of life did not improve. The bee sting therapy was well tolerated, with no significant side effects (Wesselius et al., 2005).

Ginger

The rhizome of the Zingiberaceae family, ginger, is widely used as a spice or nutritional supplement and has a long history of usage in herbal medicine (Mohd Yusof, 2016). The paradols, zingerone, shogaols, and gingerols are primarily responsible for the pharmacological actions of ginger (Prasad & Tyagi, 2015). 6-Gingerol, a pungent substance of fresh ginger, has been shown to reduce the severity of a variety of chronic diseases in both animal models and people. 6-gingerol is transformed to 6-shogaol after dehydration, which is more stable and has more potent pharmacological effects than 6-gingerol (Kou et al., 2018). Zingerone has been linked to a variety of pharmacological effects, including anti-bacterial, anti-hyperlipidamia, anti-tumorigenic, antioxidant, and anti-inflammatory properties (Choi, Kim, Jeong, & Oh, 2018).

In an experiment on the mice with EAE, an animal model of brain inflammation that causes inflammatory demyelinating illness of the CNS. The CNS expression of chemokines CCL22 and CCL20, as well as their receptors CCR4 and CCR6, has been found to be modulated by ginger extract. Since CCR4 is expressed on the surface of NK cells, Treg, Th2, and macrophages and functions as a receptor for CCL22 and CCL17, it is crucial in the pathogenesis of EAE and MS. In microglia, ginger extract or some of its derivatives have been shown to decrease the expression of inflammatory factors such as NF- κB, TNF-α, and IL-1. As a result, ginger extract may potentially serve as an indirect inhibitor of chemokine expression (Jafarzadeh, Arabi, Ahangar-Parvin, Mohammadi-Kordkhayli, & Nemati, 2017). In another research, it was also reported that the mRNA expression of IL-17, P19, and P40 in the CNS, as well as serum IL-23 levels, was dramatically reduced in EAE rats fed with ginger extract (Jafarzadeh et al., 2015). As a result, ginger extract can be used to treat MS patients.

Ashwagandha

Withania somnifera (WS), often known as ashwagandha or Indian ginseng, is a medicinal herb used for millennia due to its neuroprotective properties, across the world. In a range of neuronal and nonneuronal cells, WS extracts have been shown to decrease oxidative stress. In addition, WS extracts have been shown to inhibit SOD1 (Cu-Zn superoxide dismutase) misfolding by stimulating the synthesis of molecular chaperones that aid in the refolding of misfolded proteins or the preservation of their natural conformation.

The study found that WS therapy increased the life span of SOD1 mice. The mitochondrial chaperon Hsp60 and Hsps70 were increased in response to WS therapy. When compared to control mice, WS-treated SOD1 animals had a greater number of spinal motor neurons and ventral root axons, as well as considerably improved motor function from the start of the disease. IL-1β, IL-6, IL-4, and IL-3 levels were all significantly reduced after WS therapy. WS has been shown to reduce neuronal injury by modulating inflammation in the spinal cord (Dutta, Patel, & Julien, 2018).

Changes in glutamate homeostasis can have substantial effects on brain cells through the development of neurotoxic or excitotoxic cascades; glutamate neurotoxicity has also been linked to MS etiology. In a study, the neuroprotective effect of ashwagandha against glutamate-induced toxicity was investigated. Glutamate-induced cell death was reduced by the ashwagandha leaves derived water extract treatment, which was also able to reverse glutamate-induced alterations in HSP70 (a stress protein) to a considerable extent. It also inhibits MMP-2 and MMP-9 activity while increasing NCAM expression and cell survival, even at high glutamate concentrations (Kataria, Wadhwa, Kaul, & Kaur, 2012).

Brahmi

Bacopa monnieri, often known as brahmi, is an important herb in ayurvedic medicine. In a study, embryonic mouse hypothalamus cells and human glial (U-87 MG) cells were used to investigate the neuroprotective effects of extracts of *Bacopa monnieri* and *Rosmarinus officinalis* in combination. In hypothalamic cells, combination of brahmi and rosemary extracts shown anti-lipid peroxidation action and antioxidant properties, inhibits phospho-tau expression, inhibits synthesis of amyloid precursor protein (APP), and increases production of brain-derived neurotrophic factor (Ramachandran, Quirin, Escalon, & Melnick, 2014). Bacopa extracts have been shown to limit the production of TNF-α and IL-6 from LPS-activated microglia, resulting in a reduction in neuroinflammation, and in a cell-free assay system almost blocks the activities of caspase 1 and 3 and MMP3, regulating neuronal survival. As a result, bacopa and its components are attractive candidates for the development of new neuroinflammation-targeting therapies, with the potential to treat a variety of CNS diseases (Nemetchek, Stierle, Stierle, & Lurie, 2017).

Application to other neurological conditions

In this chapter, we have reviewed the importance of natural products in MS, as intake of diet rich in bioactive compounds with anti-inflammatory, anti-oxidative, and neuroprotective properties may reduce the severity or lower the risk of developing MS. Especially, diets rich in vitamins, polyphenols, and other natural supplements have proven pharmacological actions. Similarly, the role of these compounds in various neurological

conditions including Parkinson's disease, Alzheimer's disease, Huntington's disease, dementia, and others has also been highlighted by various experimental studies. EGCG, a major polyphenol found in green tea, exhibits the neuroprotective effects against various neurodegenerative disease including AD and PD (Jung & Kim, 2018; Pan, Jankovic, & Le, 2003; Weinreb, Mandel, Amit, & Youdim, 2004). Interestingly, Ehrnhoefer et al. revealed that EGCG directly binds to and inhibits the aggregation of neuroinhibitory polypeptides such as amyloid-beta (Ehrnhoefer et al., 2008). Another common bioactive compound, that is, resveratrol also shows anti-inflammatory and anti-oxidative roles in AD (Gomes et al., 2018; Rao et al., 2020) and PD (Kung, Lin, Kung, & Lin, 2021). It has the capacity to improve the memory and cognitive ability in these neurological disorders (Kung et al., 2021; Witte, Kerti, Margulies, & Floel, 2014; Zhang et al., 2018), which may further reduce the risk of AD and dementia (Kakutani, Watanabe, & Murayama, 2019). A recent study revealed the neuroprotective effects of quercetin against the ROS-induced oxidative stress in PD model (Ghaffari, Hajizadeh Moghaddam, & Zare, 2018). Quercetin exhibits the potential to improve the mitochondrial dysfunction (Sandhir & Mehrotra, 2013), behavioral deficits and inflammatory damages in HD models (Chakraborty et al., 2014) via their inherent property of scavenging the free radicals.

There is an accumulating evidence of using natural products/traditional medicines in the past/history, for instance, use of turmeric, curcumin, neem, and others for treatment of various diseases. Similarly, research in today's world also focuses on exploiting the therapeutic potential of natural products such as *Withania somnifera, Bacopa moreneii* in treatment of the neurodegenerative disorders. The remarkable effects of *W. somnifera* in AD pathology have been observed, as evidenced by reversion of pathological changes like accumulation of beta-amyloid peptide and behavioral changes in AD model (Jayaprakasam, Padmanabhan, & Nair, 2010; Sehgal et al., 2012). Similar pharmacological impact of WS has been observed in PD model (Ahmad et al., 2005; Prakash et al., 2014). The administration of root extract of WS in PD mice improved the physiological abnormalities and reduced the oxidative stress via enhancing the levels of cytosolic glutathione peroxidase (RajaSankar et al., 2009). A recent study by Joshi et al. demonstrated that bioactive compound from WS reduced the inflammation, activated the heat shock proteins thereby slowing-down the progression of HD (Joshi, Kumar, Kaznacheyeva, & Jana, 2021). Moreover, studies have also identified that *B. monnieri,* also known as brahmi, has a mixture of bioactive compounds that exhibit neuroprotective effects (Abdul Manap et al., 2019; Limpeanchob, Jaipan, Rattanakaruna, Phrompittayarat, & Ingkaninan, 2008; Saini, Singh, & Sandhir, 2012). It has been observed that brahmi mitigates the cognitive impairment during the course of AD via enhancing the density of cholinergic neurons (Mathew, Paul, Nandhu, & Paulose, 2010; Uabundit, Wattanathorn, Mucimapura, & Ingkaninan, 2010). Similarly, the therapeutic effects of *B. monnieri* are indicated in epilepsy (Mathew et al., 2010) and dementia (Saini et al., 2012) as well. A study by Siddique et al. using drosophila PD model

revealed that leaf extracts from *B. monnieri* reduced apoptosis, oxidative stress as well as ameliorated the behavioral impairment in PD (Siddique, Mujtaba, Faisal, Jyoti, & Naz, 2014). Taken together, it can be stated that these natural bioactive compounds show anti-inflammatory, anti-oxidative, anti-apoptotic, and neuroprotective effects. In addition, they are found to be involved in reverting the impaired cognitive functions and physiological alterations related to pathology of various neurodegenerative disorders. These findings pave the path for exploring or identifying many such natural bioactive compounds with the potential to be use as anti-neurological agents.

Other components of interest

Many extra nutritional constituents exist in food that is essential for leading a healthy life and also proven as preventive for some fatal diseases. Bioactive compounds are such components of diet present in a small quantity but appear with numerous health benefits. Several neurological disorders are characterized by neuroinflammation; the pathological condition appears with aging (Teodoro, 2019). The integrative approach to the treatment of these neurological disorders includes a healthy diet, necessary vitamins, and supplements, and medicines derived from natural products. Other natural products are involved in neuroprotection can be taken into consideration for the treatment of MS. A study was reported that the leaf of *Caryocar brasiliense* exhibits anticholinesterase and antioxidant effects., which can protect the neuron from damage due to oxidative stress and slow down neurodegeneration (de Oliveira et al., 2018). Genistein is an isoflavonoid derived from soy products, having estrogen-specific hormonal effects that can reduce oxidative stress, and regulated the transcription of cytokines thus protecting the neurons from inflammatory responses (Sharifi-Rad et al., 2020). Hespiridin is a flavanone derived from citrus fruits is found to be a potent antioxidant that strongly inhibits lipid peroxidation. It is also evident that the bioactive compound in promoting neuron survival as well as acting as a neurotrophic factor (Cho, 2006). Pieces of the literature suggest that glycosides, terpenoids, and phenolic glycosides promote neuritogenesis and enhance nerve impulse transmission. Also, these compounds protect the neuronal cells from apoptotic cell death and increase their life span during aging (Kumar, Kumar, & Naveen, 2015). Overexpression of NMDA receptor, resulting in the pathology of excitotoxicity in nerve cells, can be prevented through administration of Alkaloids derived from Tomentosa Uncaria (Kang et al., 2002). There is a well-known fact that the neuroinflammation is one of the severe pathological conditions appears in a wide range of neurological disorders. Thus, it is important to take a healthy diet that is devoid of proinflammatory food materials such as saturated fatty acids, high dietary salt intake, and a hypercaloric diet. A diet enriched with anti-inflammatory bioactive compounds is strongly suggested to take regularly, including carotenoids, polyphenols, vitamin D, and vitamin A.

Summary and conclusions

The findings of this study indicate that MS is a potentially incurable neurological disorder that is a leading cause of disabilities common in young adults. To date, several underlying cellular mechanisms involving neuronal loss have been detected that ultimately cause physical ailments. Several environmental factors and metabolic conditions are also involved in the emergence of this disease. Research is still under process to find out the prevention and therapeutics of this neurodegenerative disorder. However, recent studies have reported the importance of some immunosuppressive and immunomodulatory agents along with the use of stem cell transplantation therapy. In the virtue of knowledge from the Indigenous medicinal system, there is a possible way to find the cure with the potency of natural compounds. This study has shed light on some sort of natural bioactive compounds having significant therapeutic benefits for the prevention and treatment of MS. Natural compounds illustrating neuroprotective effects can play a dynamic role by regulating various pathways and cellular mechanisms. Furthermore, we have to consider the permeability of these compounds across the blood-brain barrier, which will be more efficient. It has been reported that antioxidant therapy can neutralize the hazardous effects of free-radical-mediated oxidative stress to limit the mitochondrial dysfunctions and glutamate excitotoxicity in the MS patients. Future works will look into the discovery of healthy living, and these bioactive compounds conjugated nanoparticles for drug delivery in brain. There are some findings suggest that nutritional interventions could ameliorate the symptoms of MS and reduce the neuroinflammatory responses. However, no concrete study reveals that a particular diet has a greater impact in reducing the chances of developing MS. These are the complimentary for improving lifestyle, not an alternative therapy. Based on the literatures supporting the positive impact of natural compounds on MS and neuroinflammation, synthesis of nanoparticles loaded with these compounds may have a promising preventive and therapy for MS.

Mini dictionary

Acupuncture: A traditional Chinese medicinal system where the acupressure points are stimulated via puncturing through hair-like thin needles to relieve discomfort associated with various diseases.

Astrogliosis: Abnormal increase of astrocytes in response to infection, trauma, and injury to CNS.

Demyelination: Destruction of the myelin sheath of neurons due to an auto-immune response.

Dyspnea: Breathing shortness.

Excitotoxicity: It is also known as "glutamate excitotoxicity," a process of nerve cell damage and apoptosis induced by excessive L-glutamate and subsequent influx of Ca^{2+}.
Molecular chaperons: Proteins that help in proper folding and unfolding of proteins and other macromolecular structures.
Neuroinflammation: On the onset of neurological disorders, brain's innate immune system triggers inflammation in response to injury, infection, exposure to toxins, disease, or aging.
Palpitations: A noticeable sensation especially pertaining to heart characterized by irregular heartbeat.
Relapse rate: The frequency of reappearance of a disease with its signs and symptoms after a short period of recovery.
Spasticity: A symptom caused by damage to nerves in various neurological disorders involving muscle stiffness.

Key facts

- Globally, more than 2.8 million people are affected by MS.
- Women are more susceptible to this disease than to men.
- MS is a deadly disease involving higher relapse rate and symptoms may vary.
- It affects CNS, attacks myelin sheath leading to loss of neuronal communication.
- Vitamin D levels also have a major role in pathogenesis of MS.
- Natural products with anti-inflammatory, anti-oxidative properties might slowdown the progression of MS.

Summary points

- Interferon-β lowers the relapse rate and progression of the disease.
- Combined supplementation of Vitamin D and Omega-3 fatty acids plays an anti-oxidative and anti-inflammatory role thereby lowering the relapse rates.
- The flavonoids quercetin and EGCG have the ability to cross the BBB and repairing the impaired neurons.
- High dose of Vitamin B12 improves the pathologically altered visual and auditory functions.
- Therapeutic administration of bee venom in MS patients improves the control and coordination of body and reduces numbness and muscle stiffness.
- *W. somnifera* and *B. monnieri* have the ability to suppress the proinflammatory cytokines such as IL-1β, IL-6, TNF-α, etc., thus exhibiting the neuroprotective effects.

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